HEMORRHAGIC FEVERS

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Infectious Diseases

Objectives

- Status of emerging infections in the tropics
- Pathophysiology, host-parasite relationships and known life cycles
- Arboviruses
- Hemorrhagic Fevers
- Treatment and preventive measures

Zoonoses

- Zoonoses are infections that are transmitted in nature between vertebrate animals and humans.
- Criteria
  - Vertebrate reservoir exclusive of humans
  - Transmission
  - Infectious disease syndrome in humans

Transmission

- Directly to people
- From products of host animal
- Through arthropod intermediate

Hemorrhagic Fevers

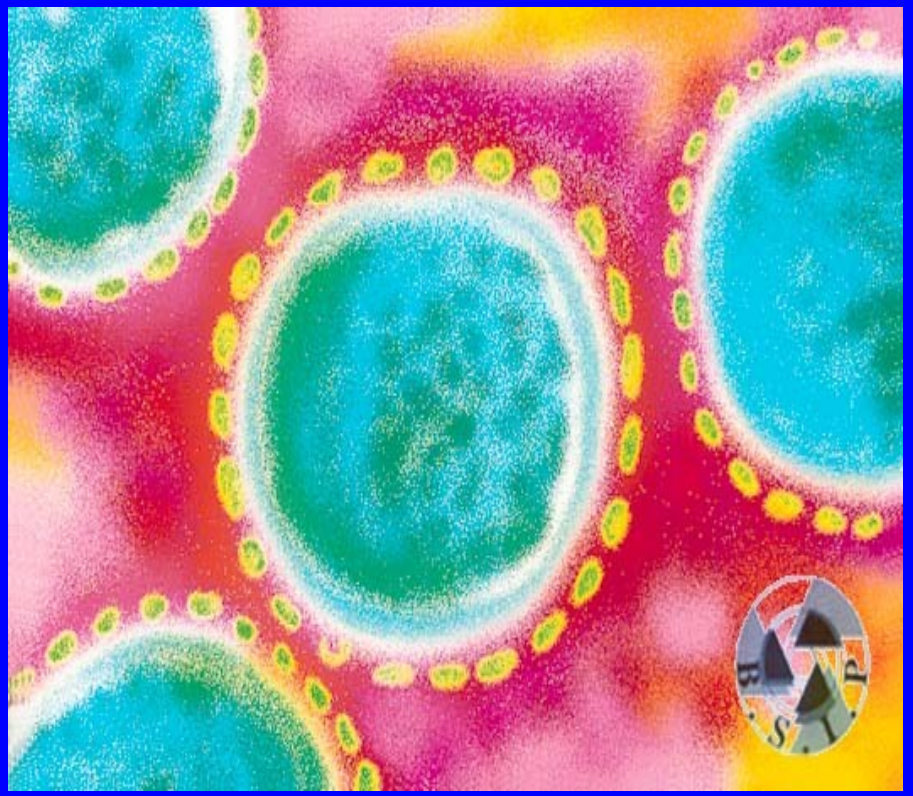
- Bunyaviridae
  - HFRS, RVF
- Arenaviridae
  - Lassa fever
- Flaviridae
  - Dengue (DHF), Yellow fever
- Filoviridae
  - Ebola, Marburg

Pathogenesis and Manifestations

- Endothelial cell damage/capillary leak
- Platelet dysfunction
- Cytokines and other soluble mediators of shock and inflammation
- Petechiae, ecchymoses, mucous membrane hemorrhages

Bunyaviridae

- 5 genera
- 250 species
- Enveloped RNA virus



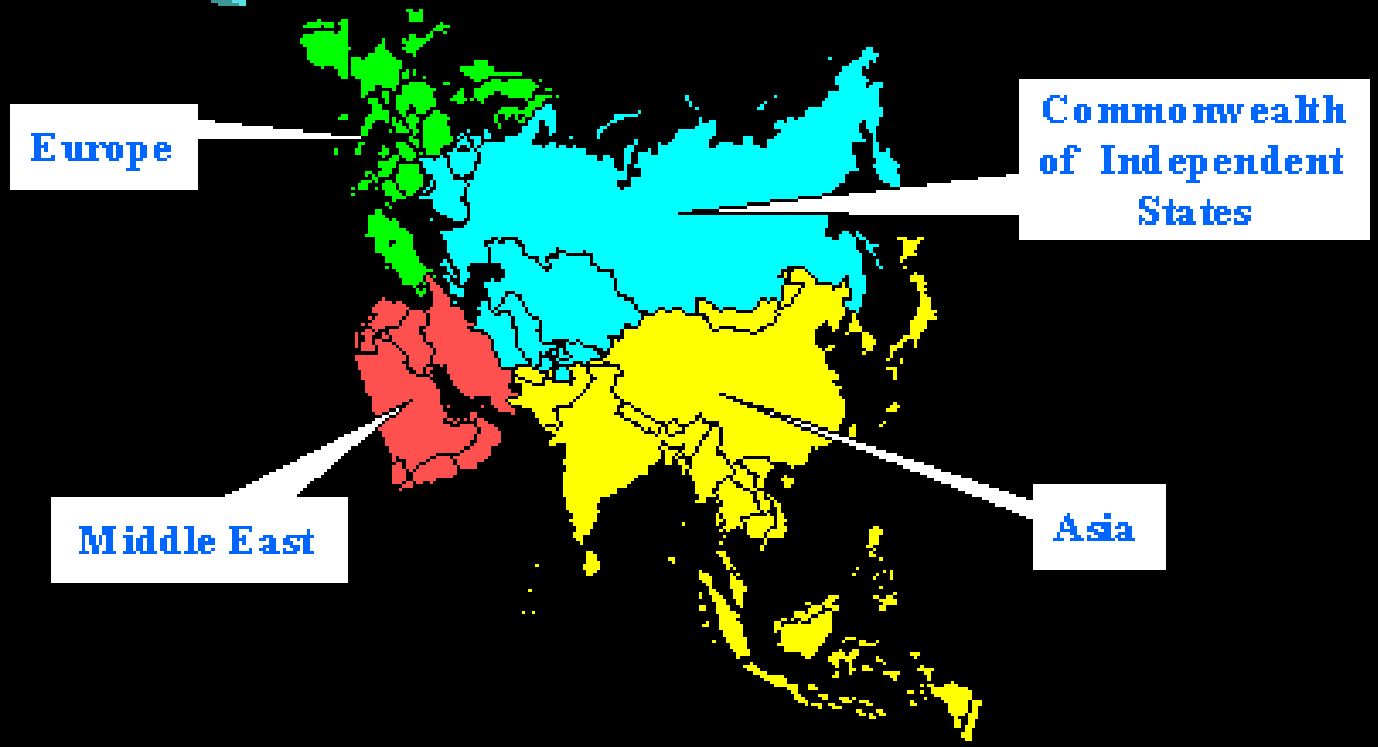
Hantaviruses

- Family *Bunyaviridae*
- Enveloped viruses with RNA genome
- Replicate exclusively in the host cell cytoplasm
- Entry into cell is thought to occur by attachment of virions to cellular receptors and subsequent endocytosis
- New and Old World viruses

Old World Hantaviruses

- Associated in Europe and Asia
- Associated with specific rodent hosts
- 4 genetically distinct Hantaviruses
- Hantaan - Asia
- Seoul - World-wide
- Dobrava - The Balkans
- Puumala - Scandinavia, Russia, Europe

Europe - Asia - Middle East



KHF/HFRS

- Epidemic hemorrhagic fevers during military campaigns
- Korean Conflict saw 3000 United Nations troops with hemorrhagic fever associated with renal failure and shock
- Regional distributions of hemorrhagic fever with renal syndrome (HFRS)

US Marines in ROK

- US – Korean military joint field exercise
- Late September to mid-November 1986
- 14 cases of KHF among 3,754 US Marines
- 10 were hospitalized & 2 died (CFR = 14%)
- Cases confirmed by serologic testing and post deployment screening of serum from 2053 personnel
    - MMWR Feb 19, 1988/37(6);87-90,95-6

Case Presentations 1986

- The four nonhospitalized US Marine patients had a variety of symptoms
- The ten hospitalized US Marine patients had:
  - Fever (100%)
  - Fatigue (100%)
  - Thrombocytopenia (100%)
  - Proteinuria (100%)
  - Headache (90%)
  - Conjunctival injection (90%)

ROK Military Forces 1986

- ~ 150 cases of KHF were reported among ROK military forces between September and December 1986
- 9 cases were identified at the same time of the US Marine outbreak
- No deaths

KHF - Hantaan Virus

- Presents with the most severe clinical form
- Endemic in Asia
- Manchurian striped field mouse *Apodemus agrarius*

KHF - Hantaan Virus

- Transmission - infective aerosols
- Rat urine and other excreta
- Rarely by rodent bites
- Nosocomial or person-to-person transmission has not been reported
- Very difficult to culture virus from infected persons

Hantaan Virus Epidemiology

- China - 60,000 to 150,000 cases reported each year
- Most cases in Korea, China and Japan
- Three environments:
  - Rural: farmers, construction workers, soldiers
  - Urban: Rattus sp. transmitting Seoul virus
  - Animal Room: infected experimental rodents

KHF - Hantaan Virus

- Diagnosis
  - Antibody detection with ELISA assays - the standard for serological diagnosis
  - Immunohistochemical testing of formalin-fixed tissues with monoclonal and polyclonal antibodies
  - RT-PCR to detect Hanta viral RNA in fresh-frozen lung tissue or blood clots

Clinical Manifestations of HFRS

- Considerable variation in the incidence of various manifestations and the severity of the individual phases
- Puumala virus has the mildest form
  - no shock
  - phases can be skipped
  - hemorrhagic manifestations can be absent

Phases of HFRS

- Incubation Phase - 16 days
- Febrile Phase - 5 days
- Hypotension Phase- 2 days
- Oliguric Phase - 5 days
- Diuretic Phase - 5 days
- Convalescent Phase - 25 days

Clinical Manifestations of HFRS

- Febrile Phase
  - abrupt onset
  - fever, chills, lethargy and weakness
  - frontal or retro-orbital headache, blurred vision
  - myalgia and lumbar aching
  - diffuse abdominal pain, nausea and vomiting

Clinical Manifestations of HFRS

- Hypotensive Phase
  - shock or hypotension during the last 24-48 hours of the febrile period
  - 1/3 of deaths occur in this phase

Clinical Manifestations of HFRS

- Oliguric Phase
  - blood pressure normalizes
  - brief periods of hypertension
  - oliguria - diminished urine output of less than 500 ml urine per 24 hours
  - continued nausea and vomiting
  - overall severity of the disease is reflected in the oliguric phase (2/3 of overall deaths)

Clinical Manifestations of HFRS

- Oliguric Phase
  - 15% develop hemorrhagic manifestations
    - epistaxis
    - ecchymosis
    - subconjunctival hemorrhage
    - gross hematuria
    - hemoptysis
    - CNS and GI bleeding

Clinical Manifestations of HFRS

- Diuretic Phase
  - progressive improvement when diuresis starts within 2 weeks of onset of disease
  - major fluid and electrolyte shifts occur
  - need to replace fluids and electrolytes accordingly

Clinical Manifestations of HFRS

- Convalescent Phase
  - usually asymptomatic
  - may see polyuria and loss of urine concentrating ability
  - long-term sequelae
    - renal tubular acidosis, renal hypertension, proteinuria, end-stage renal disease
    - empty sella syndrome

Differential Diagnosis for HFRS

- Easy to diagnose when in an epidemic of classical polyphasic hemorrhagic renal syndrome in Asia
- Looks like:
  - leptospirosis, scrub typhus, dengue fever, and other mild febrile viral illnesses
  - renal vein thrombosis

Treatment of HFRS

- Supportive
- Strict management of fluid and electrolytes
  - prevent fluid overload in the early stages
  - keep up with fluid losses during the diuretic phase
  - dialysis can be life-saving
  - steroids not proven efficacious

Treatment of HFRS

- IV ribavirin therapy in a double-blind, concurrent, placebo-controlled trial resulted in a sevenfold reduction in Hantaan virus-associated HFRS mortality when administered within 6 days of fever onset
  - Huggins JW, Hsiang CM, Cosgriff TM, et al: Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. J Infect Dis 164:1119, 1991.

Ribavirin (Virazole)

- Guanosine analog that inhibits the replication of a wide range of RNA and DNA viruses:
  - myxo-, paramyxo-, arena-, bunya-, herpes-, adeno-, pox-, retroviruses and RNA tumor viruses
  - interferes with synthesis of GTP and thus nucleic acid synthesis

Ribavirin (Virazole)

- Renal excretion accounts for ~ 40% of ribavirin's clearance
- Systemic ribavirin causes dose-related and reversible anemia
- Ribavirin is teratogenic, embryotoxic, mutagenic, tumor-promoting and gonadotoxic

Treatment of HFRS

- IV ribavirin therapy
  - most effective when given within first 6 days of illness
  - Administer IV with 30 mg/kg loading, then 15 mg/kg every 6 hours for 4 days, then 8 mg/kg q 8h for an additional 6 days
  - contraindicated in pregnancy
  - pregnant women should not provide care

Treatment of HFRS

- Ribavirin Therapy
  - reduced kidney damage & ↑ Creatinine Clr.
  - decreased days of hypotension
  - decreased duration and magnitude of hypertension
  - decreased hemorrhagic manifestations
  - earlier onset of recovery
  - only side effect is a reversible anemia

Mortality of HFRS

- 5-15% of Hantaan virus-associated disease
- <1% for Puumala virus-associated disease
- Untreated patients have a seven fold greater risk of dying

Immunization

- Humoral response alone seems sufficient
- Cell-mediated response also protective
- A formalin-inactivated Hantaan virus vaccine from infected suckling mouse brain is commercially available
- Korean made; rodent brain - derived product
- Does not elicit good neutralizing antibody responses
- Only provisionally licensed in Korea
- Not FDA licensed

Immunization

- Phase II human trials with a recombinant vaccinia virus no longer being pursued because of poor results in vaccinia preimmune individuals
  - McClain, DJ, Summers P, Harrison, S, Schmaljohn, AS and Schmaljohn, CS. (1999). Phase I and Phase II Clinical Evaluation of a Vaccinia-Vectored Hantaan Virus Vaccine. J Med Virol. 60:77-85.
- Early studies with a DNA vaccine shows positive results.
  - Hooper, JW, Kamrud KI, Elgh, F, Custer, D and Schmaljohn, CS. (1999). DNA vaccination with hantavirus M segment elicits neutralizing antibodies and protects against Seoul virus infection. Virology 255:269-84.

Prevention of KHF

- Reduce the frequency of rodent-human interactions
  - applies to all rodents
  - nearly impossible in a rural setting
  - prevent access to domestic settings
  - heat, acid pH, detergents, formalin and lipid solvents will inactivate the viruses

Prevention of KHF

- Each individual must participate in unit sanitation effort
- Maintain garbage and other odiferous decaying matter in tightly closed containers
- Bury, burn or remove garbage
- Avoid inhaling dust
- Maintain rodent control measures

Arenaviridae Family

Virus	***Disease***	***Geography***
Lassa	Lassa fever	West Africa
Junin	Argentine HF	Argentina
Machupo	Bolivian HF	Bolivia
Guanarito	Venezuelan HF	Venezuela
Sabia	Brazilian HF	Brazil

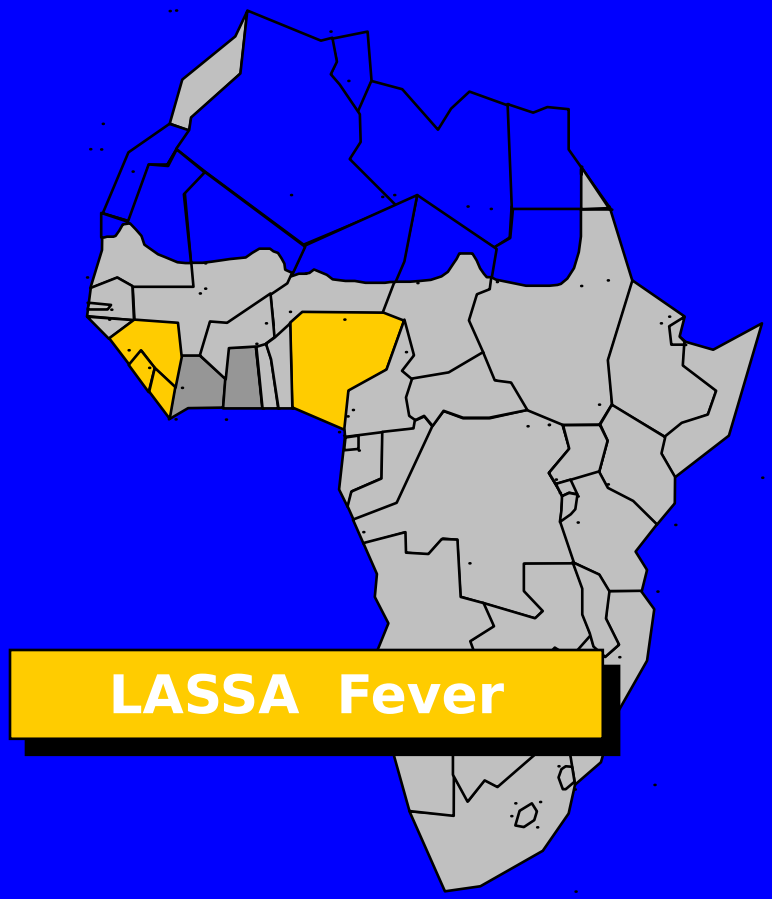
Lassa Virus

Image source: C.S. Goldsmith and M. Bowen (CDC).

Lassa Fever - Epidemiology

- Endemic in West Africa, including Nigeria, Liberia, Sierra Leone, and Guinea
- Estimated 300,000-500,000 infections/year, with 5000 deaths
- Rodent-to-human transmission (*Mastomys* species-complex)
- Secondary human-to-human transmission with the potential for nosocomial outbreaks with high case-fatality

Known Distribution of *Mastomys*



MASTOMYS **DISTRIBUTION**

Transmission

- Human-to-human:
  - Direct contact with blood, tissues, secretions or excretions of infected humans
  - Needle stick or cut
  - Inhalation of aerosolized virus

Lassa Fever- Clinical Manifestations

- Incubation period of 5-21 days
- Gradual onset of fever, headache, malaise and other non-specific signs and symptoms
- Pharyngitis, myalgias, retro-sternal pain, cough and gastrointestinal symptoms typically seen
- A minority present with classic symptoms of bleeding, neck/facial swelling and shock
- Case fatality of hospitalized cases: 15-20%
- Particularly severe in pregnant women and their offspring

Treatment

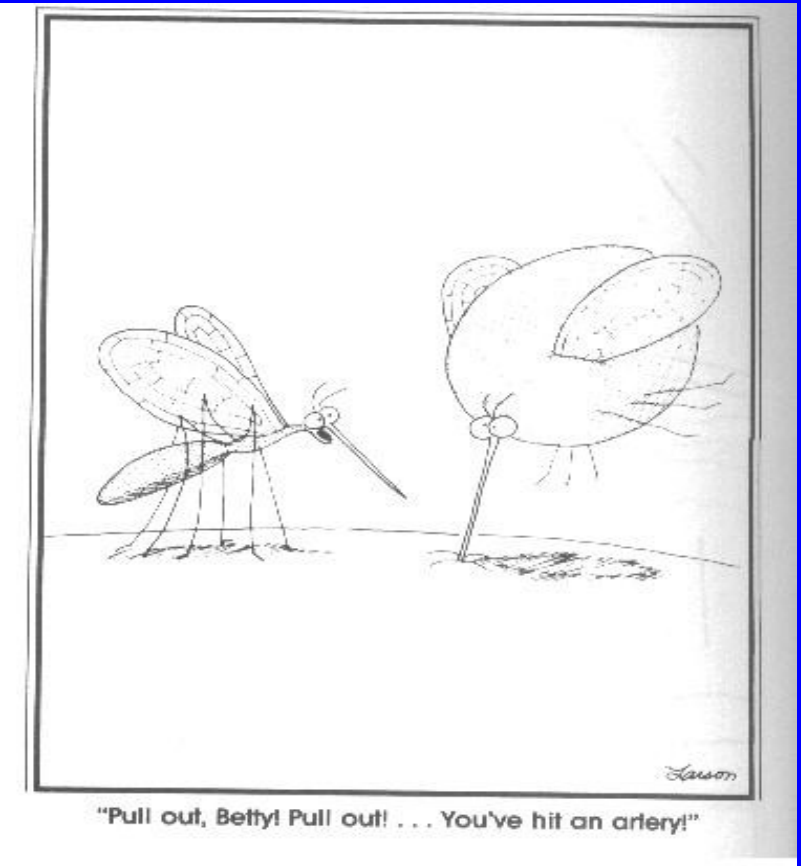
- Supportive measures
- Ribavirin
  - Most effective when started within the first 6 days of illness
  - Major toxicity: mild hemolysis and suppression of erythropoesis. Both reversible.
  - Presently contraindicated in pregnancy, although may be warranted if mother's life at risk
  - Does not appear to reduce incidence or severity of deafness

Prevention and Control

- Village-based programs for rodent control and avoidance
- Hospital training programs to avoid nosocomial spread
- Specific antiviral chemotherapy (ribavirin)

Arboviruses

- AR - ARthropod
- BO - BOrne



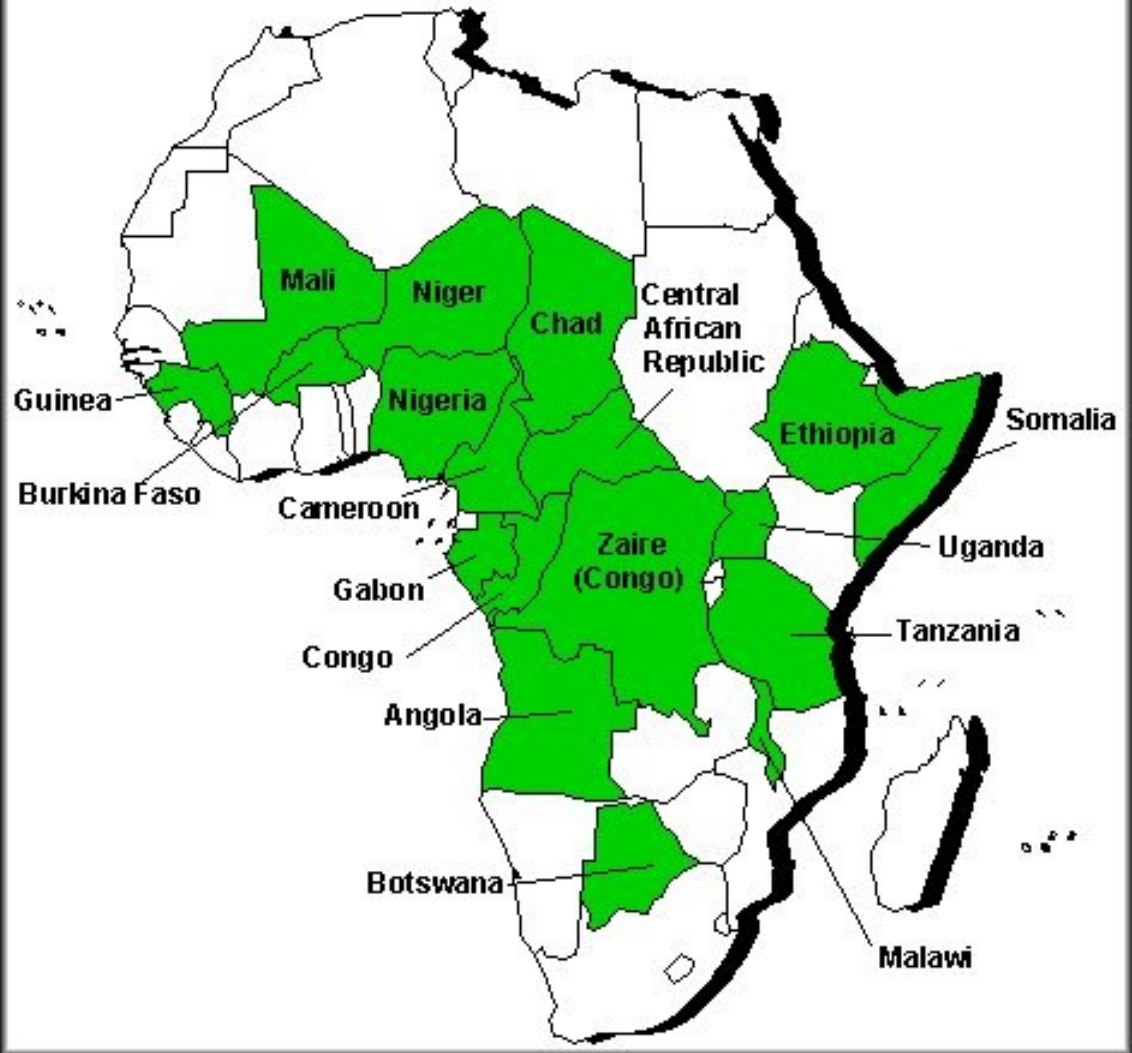
Bunyaviridae Family

Genus	Disease
Bunyavirus	LaCrosse encephalitis
Phlebovirus	Rift Valley Fever
Nairovirus	Crimean- Congo HF
Hantavirus	HPS, HFRS

Rift Valley Fever

- Zoonosis in Africa - rare VHF
- 2000 - 1st outbreak outside African continent
- Yemen - 653 suspected cases and 80 deaths
- Saudi Arabia - 443 cases with 85 deaths
- Spread into a virgin territory vs. first detection of an endemic virus in the Arabian Peninsula

African countries with lesser outbreaks of RVF, periodic isolations of virus, or serologic evidence of RVF.



Chain of Infection - RVF

- Agent - Phlebovirus
- Reservoir - Domestic ungulates; sheep, goats, cattle, and camels
- Transmission
  - Vehicle - *Aedes mcintoshi*
  - Route - Mosquito bite
- Host - Humans
- Syndrome - RVF

Clinical Manifestations - RVF

- Most - subclinical infections or mild self-limited febrile illnesses
- Severe cases
  - Incubation period 2-6 days
  - Sudden onset of fever, headache, myalgia, and backache
  - Retinitis (15%)- macular or perimacular
  - Hemorrhagic fever (1%)
  - Encephalitis (1%).
  - Case-fatality rate for VHF- 50%

RVF - Treatment

- Supportive
- Intravenous ribavirin may be considered

Flaviviridae Family

Virus	Disease
Dengue	Hemorrhagic fever
Yellow Fever	Hemorrhagic fever Hepatitis
West Nile Virus	Encephalitis
Japanese	Encephalitis

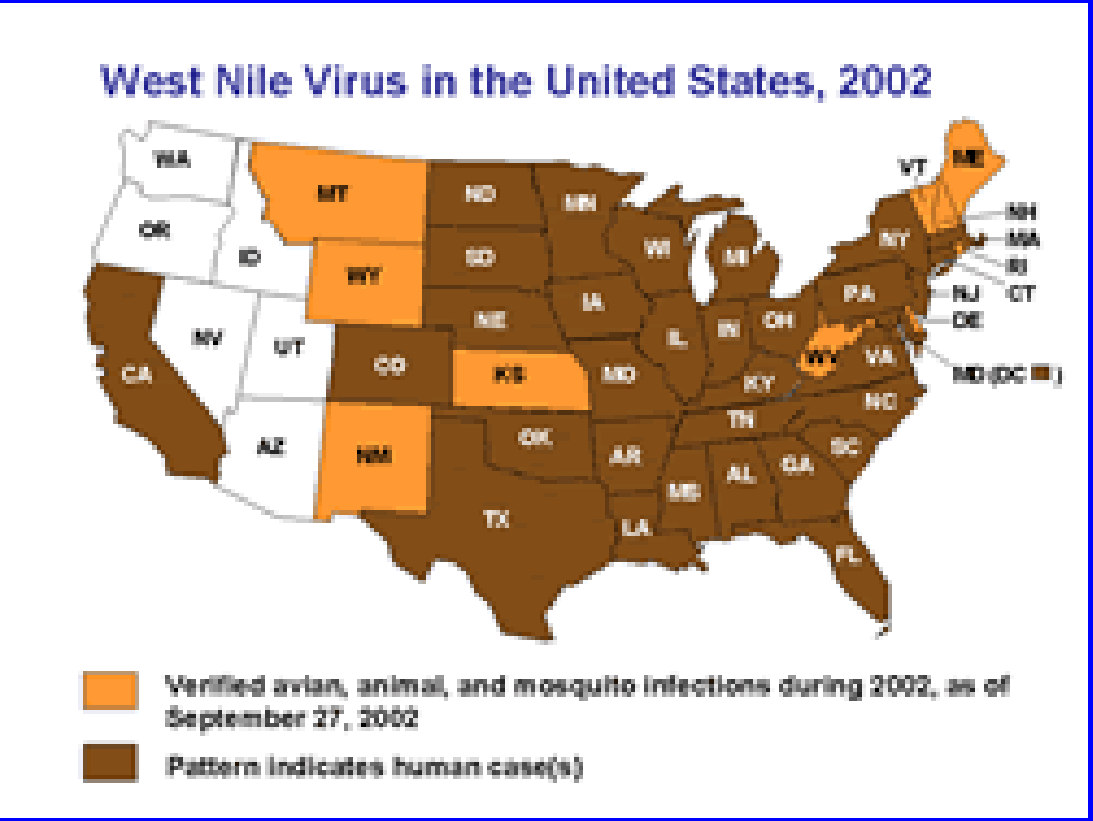
Ecological Factors

- Population movements into new arthropod habitats
- Deforestation - new forest-farmland margins
- Irrigation systems
- Uncontrolled urbanization - vector breeding
- Long-distance air travel
- Long-distance livestock transportation
- New routing of long-distance bird migration

Chain of Infection- Flaviviridae

- Agent - Flaviviridae
- Reservoir - Birds, mammals
- Transmission
  - Vehicle - mosquitoes, ticks
  - Route - arthropod bite
- Host - humans
- Syndrome – Viral Hemorrhagic Fever, viral encephalitis

West Nile Virus



Vectors: *Culex sp.* mosquitos and birds

West Nile Virus

- Antigenically related to JE and StLE viruses
- Infection usually a simple febrile illness
  - Infection to case ratio of 300:1
- Elderly most prone to worst complications
  - Viral encephalitis
  - Myelitis
  - Aseptic meningitis

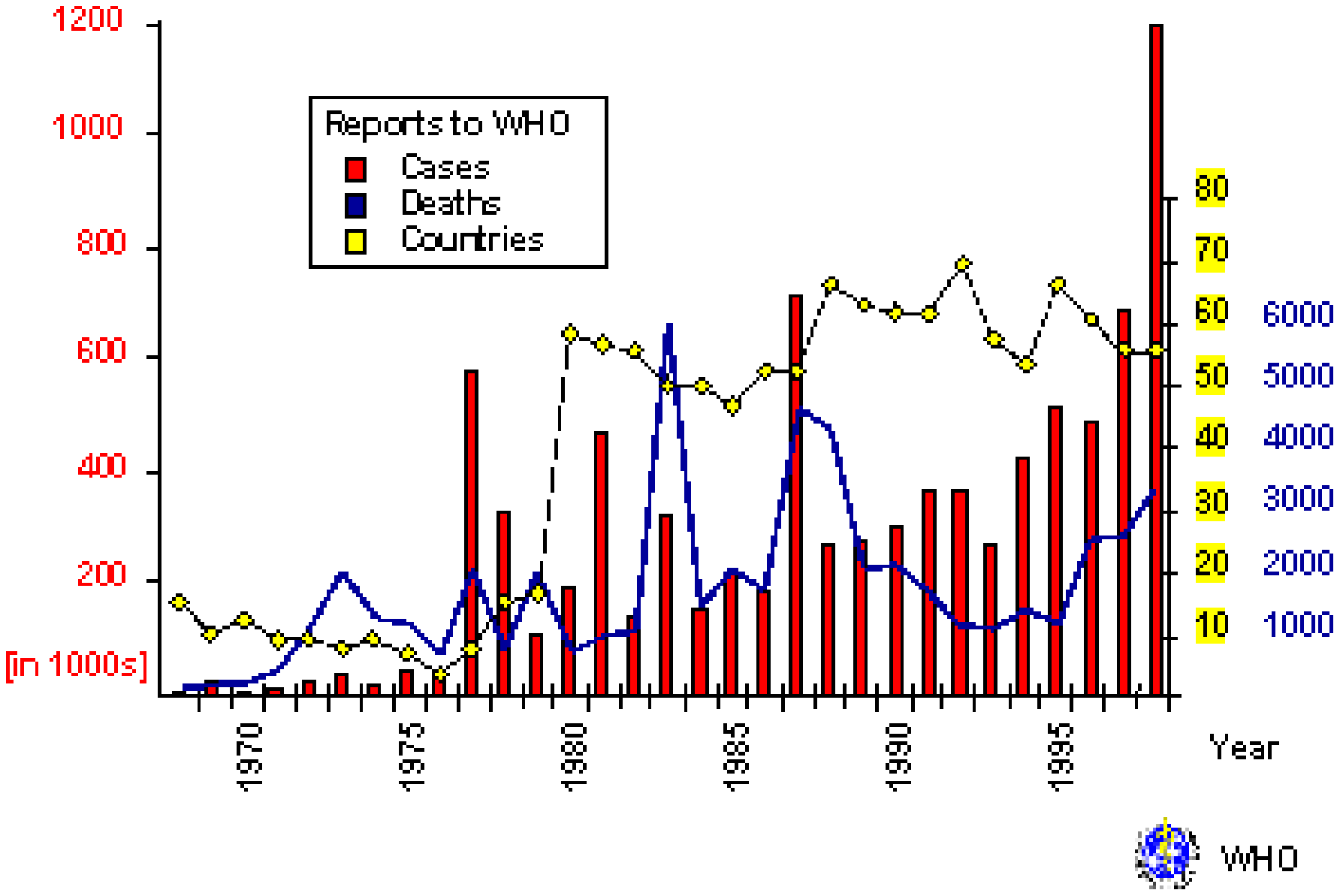
Dengue

- Flavirus
- 4 distinct serotypes – Types 1,2,3,&4
- Classic dengue fever during initial infection
- Dengue hemorrhagic fever - dengue shock syndrome (DHF-DSS) during 2nd infection with different serotype
- Dengue 2,3, & 4 generally milder than Dengue 1

Chain of Infection - Urban Dengue

- Agent - Dengue virus
- Reservoir - Humans
- Transmission
  - Vehicle - *Aedes aegypti*
  - Route - Mosquito bites
- Host - Humans
- Syndrome - Classic Dengue Fever, Dengue Hemorrhagic Fever- Dengue Shock Syndrome (DHF-DSS)

Dengue/Dengue Haemorrhagic fever
World-wide (1968 - 1998)



WHO

Dengue Fever - Initial

- Incubation - 2-7 days
- Onset - Sudden onset of frontal or retroorbital HA, backache, myalgia, arthralgia
- Dengue facies - Conjunctival suffusion, flushing, eyelid puffiness
- Transient macular, generalized rash

Dengue Fever - 2-6 days

- Nausea and vomiting
- Generalized lymphadenopathy
- Cutaneous hyperesthesia or hyperalgesia
- Palmar edema
- Taste aberrations
- Defervescence - generalized morbilliform rash

DENGUE
Clinical Aspects

- The fever is characterized as “saddleback”:
  - initial phase lasting 2 - 7 days
  - normal temperatures for 12 to 24 hours
  - rebound fever lasting several more days
- Relative bradycardia with the fever
  - normally see increase in pulse rate by 10 bpm for each degree rise in temperature (˚F)

Dengue Fever - Any Stage

- Petecchiae - common
- Purpura - common
- Epistaxis
- GI bleeding
- Menometrorrhagia
- Bradycardia

Dengue - DHF-DSS

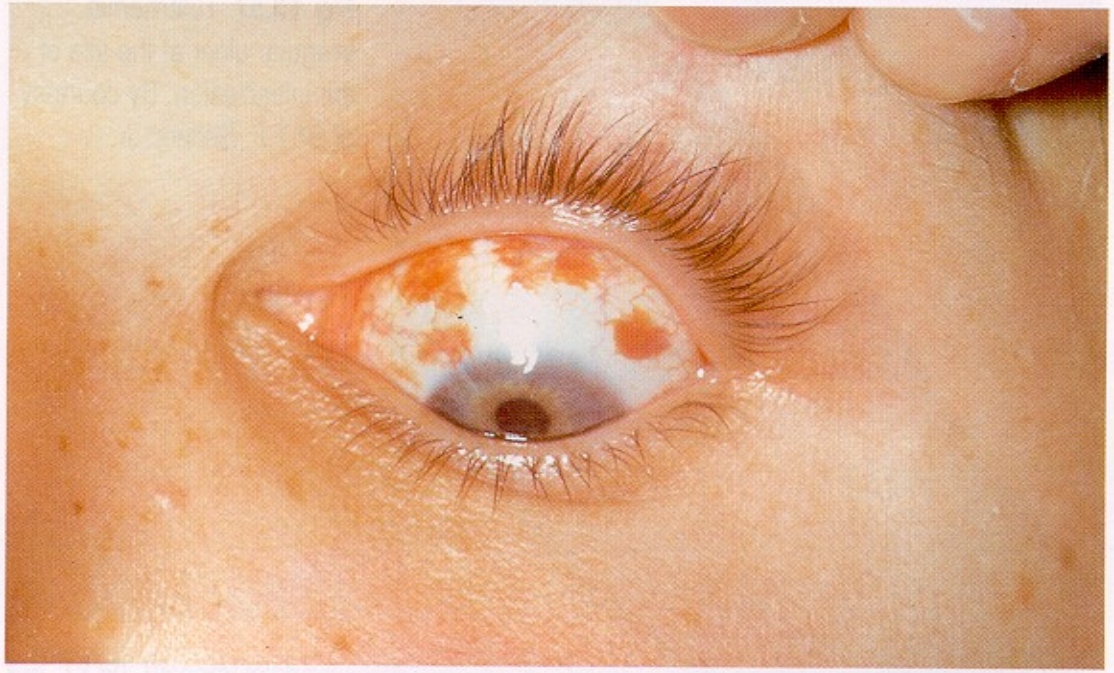
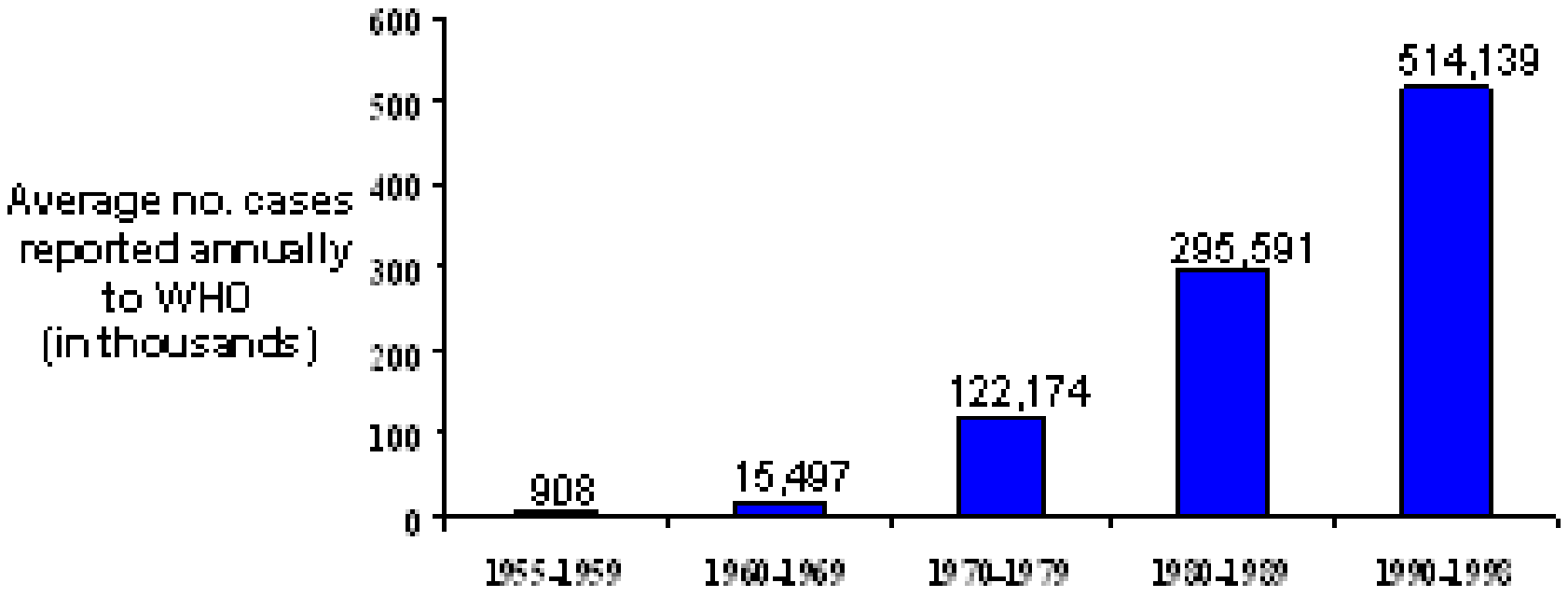


Fig. 13.54 Dengue haemorrhagic fever. Scleral haemorrhage.

Dengue - DHF-DSS

Fig. 13.53 Dengue haemorrhagic fever. Petechial rash.

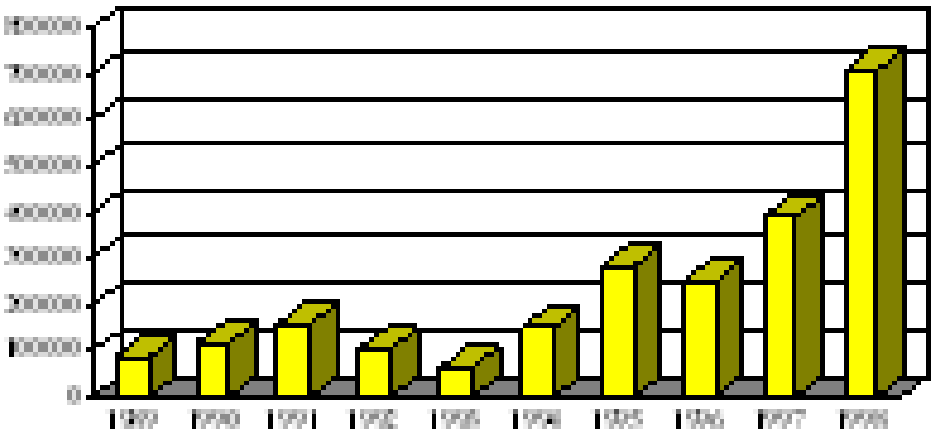
Rapid Increase of Dengue/Dengue Hemorrhagic Fever



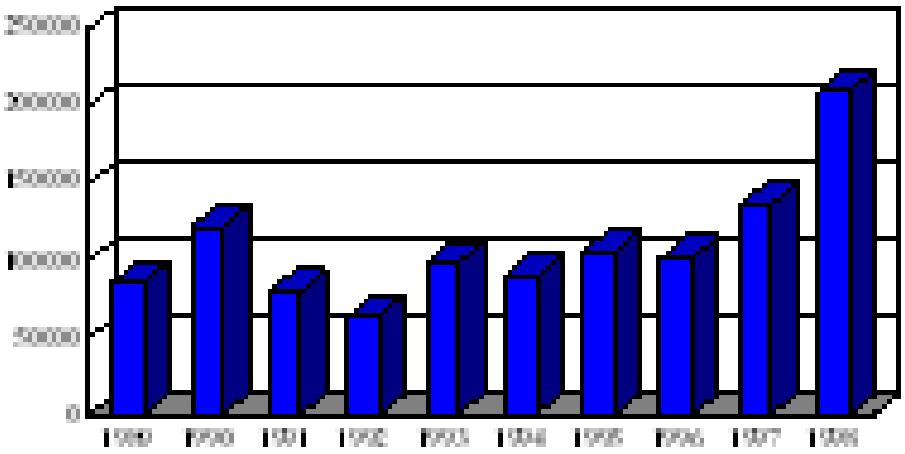
WHO

Reported Cases of Dengue/DHF

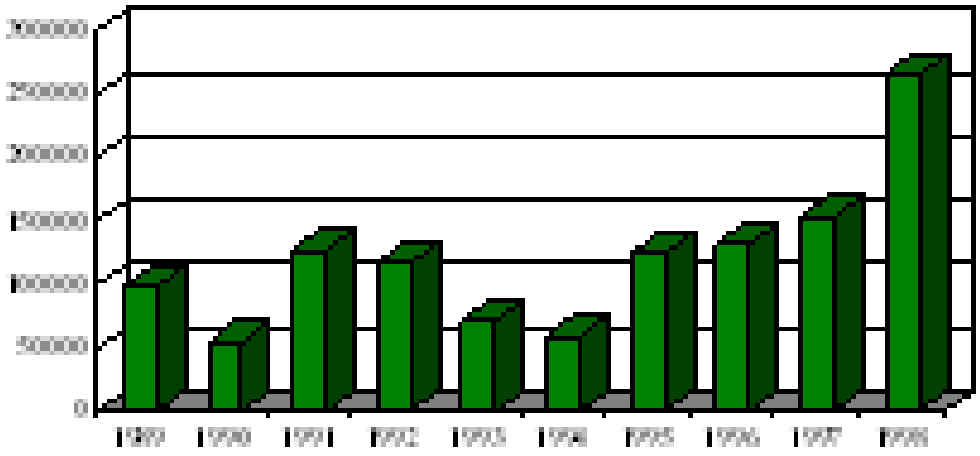
Americas Region



South-East Asia Region



Western Pacific Region



WHO

Dengue - DHF-DSS

- DHF - increased capillary permeability
- DSS - hypotension or narrow pulse pressure
- Hemoconcentration- HCT 20% > normal
- Thrombocytopenia < 100,000
- Hepatomegaly
- Ecchymoses, GI bleeding

DENGUE HEMORRHAGIC FEVER

- Primarily seen on children under 15 yo
- Sudden onset of fever with 2 to 7 days incubation
- Nonspecific signs and symptoms
- Difficult to distinguish Dengue from DHF and other tropical illnesses during the acute phase

DENGUE SHOCK SYNDROME

- Shock caused by plasma leakage
- Somnolent, petechiae on face, perioral cyanosis
- Hypotension, narrow pulse pressure, rapid weak pulse
- Labs: thrombocytopenia, leukopenia, elevated LFTs, hemoconcentration

DHF-DSS - Treatment

- Supportive
- IV fluids - reduce when capillary permeability resolved
- Blood transfusions as needed
- Analgesics
- Sedatives

DHF/DSS TREATMENT

- Early diagnosis
- Aggressive fluid replacement
- Extravasated fluid is rapidly absorbed during recovery - ↓ Hematocrit
- Transient functional vascular changes are probably due to a short-acting mediator
- Untreated - 30% mortality

DHF/DSS PATHOGENESIS

- Controversial
- Two theories - probably both are correct
- No good animal models
  - primates have infection but no disease

DHF/DSS PATHOGENESIS

- Secondary infection or immune enhancement hypothesis
  - prior infection
  - antibody-dependent enhancement of infection
  - mononuclear cell lineage secrete vasoactive mediators
  - leading to increased vascular permeability and hypovolemia

DHF/DSS PATHOGENESIS

- Genetic Selection Pressure hypothesis
  - replication leads to error and variation in RNA
  - some virus strains have greater epidemic potential
  - increased virus replication and viremia
  - increased severity of illness

DHF/DSS PATHOGENESIS

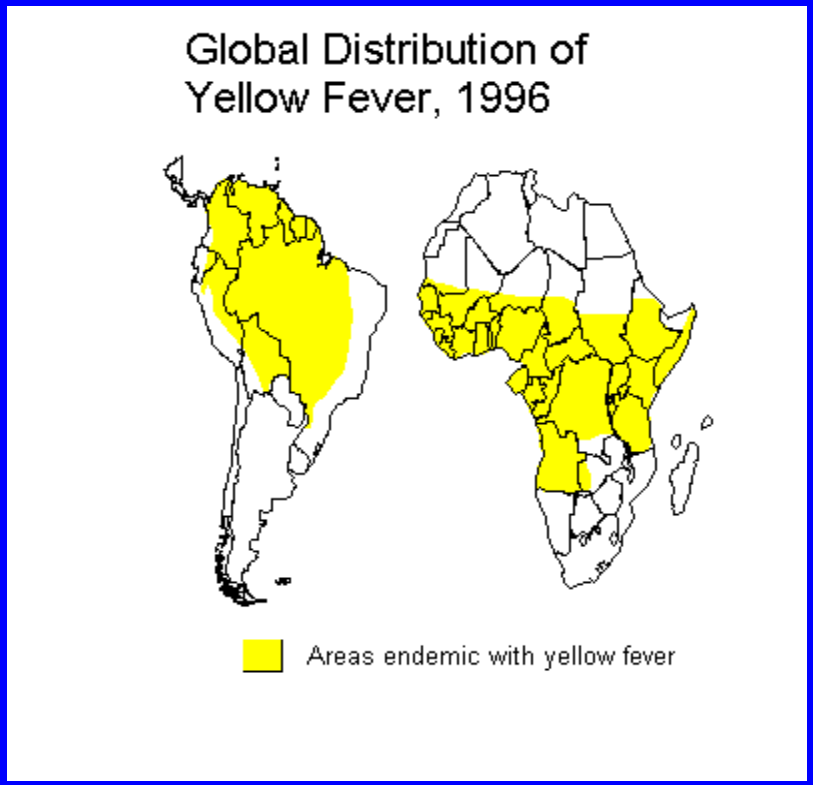
- Host Immune factors
  - 90% of patients with DHF have a secondary infection
  - a pre-existing dengue antibody is a risk factor for DHF
  - unknown mechanism for the increased vascular permeability seen
    - cytokines
    - TNF
    - gamma-Interferon

Yellow Fever Virus

- African origin to the New World - 1648
- Transmitted by *Aedes aegypti* mosquito
- Rare cause of infection for travelers and the military due to very effective live virus vaccine

Distribution of Yellow Fever

- South America
  - Sporadic infections in forestry and agricultural workers
  - 100 cases/year
- West and Central Africa
  - during rainy season
  - Occasional outbreaks in urban locations
  - 200,000 cases/year



Yellow Fever
Pathophysiology

- Data inferred from attenuated 17d virus vaccine studies
- TNF-α, Il-1ra and IL-6 from 2-7 days
- Lymphocytopenia
- Hepatocellular damage
- Kidney hemorrhages and acute tubular necrosis
- Myocarditis
- Neutralizing antibodies clear the infection
- Lifelong immunity

Yellow Fever

Clinical Features

- Broad range of severity
  - Self-limited grippe
  - Hemorrhagic fever with 50% fatality
- Incubation period of 3 – 6 days
- Fever, headache, myalgias, conjunctival injection, facial flushing, and a relative bradycardia

Yellow Fever

Clinical Features

- Remission of fever for hours to days
- Renewed symptoms with high fever, headache, LS back pain, nausea, vomiting, abdominal pain, and somnolence
- Icteric hepatitis
- Hemorrhage
  - GI, oral/nasal mucosa, petechiae/purpura
- Hypotension, shock and metabolic acidosis
  - Myocardial dysfunction and arrhythmias
- Death in 7 – 10 days for 50% of critically ill
- Recovery with no chronic hepatitis

Yellow Fever Vaccine

- Live attenuated virus (17D strain) [Theiler 1930]
- Prolonged protection after single dose (>10 days for 95%)
- Immunization boosters every ten years
- PHS Form-731 International Certificate of Vaccination
  - Valid ten days post-immunization
  - Valid for ten years
- For children > 4 months (prefer > 9 months)
- Contraindicated in pregnancy and those with cell-mediated immune deficiency
- HIV would not be an absolute contraindication
  - 17 - 77% antibody response

Legally Required Vaccination

- Give a medical waiver if needed
- Use the official stamp

Yellow Fever Endemic Countries

Countries in Africa			Countries in South America
Angola	Gabon	Rwanda	Bolivia
Benin	Gambia	Sao Tome &	Brazil
Burkina Faso	Ghana	Principe	Colombia
Burundi	Guinea	Senegal	Ecuador
Cameroon	Guinea-Bissau	Sierra Leone	French Guiana
Central African	Kenya	Somalia	Guyana
Republic	Liberia	Sudan	Panama
Chad	Mali	Tanzania	Peru
Congo	Mauritania	Togo	Suriname
Cote d'Ivoire	Niger	Uganda	Venezuela
Djibouti	Nigeria	Zaire	
Equatorial		Zambia	
Guinea			
Ethiopia			

New, Emerging and Reemerging Infectious Diseases

- Advent of new virus
  - Novel mutations
  - Gradual evolution
- Dissemination in human population
  - Changes in behavior
  - Changes in environment

Filoviridae

- Severe viral hemorrhagic fever (VHF)
- Morphology - threadlike
  - Filo - Latin “filament”
- Single strand RNA
- Two species
  - Marburg
  - Ebola: Sudan, Zaire, Ivory Coast, & Reston species
- Stable at room temperature for several hours

Filoviruses

- Natural history - source unknown
  - Suspect reservoirs - spiders, soft ticks, bats, monkeys
- Transmission
  - Index case - unknown
  - Secondary cases
    - Parenteral inoculation - high mortality
    - Skin or mucous membrane - most human cases
    - Aerosol - not established

Marburg Virus

- Rare, severe hemorrhagic fever
- Lab outbreaks in 1967 in Marburg & Frankfurt, Germany and Belgrade, Serbia
- 37 became ill
- Source: African Green monkeys

Ebola Virus

- Filament structure
- Affects humans, monkeys and chimpanzees
- Sporadic outbreaks
- 30% mortality with medical care-givers
- Overall – 60 - 90% mortality (age/gender)

Ebola Virus Symptoms: 1-3 Days

- High fever
- Headache
- Muscle aches
- Stomach pain
- Fatigue
- Diarrhea
- Sore throat
- Hiccups
- Rash
- Red and itchy eyes
- Vomiting blood
- Bloody diarrhea

Ebola Virus Symptoms: One Week

- Chest pain
- Blindness
- Bleeding
- Shock
- Death

Filoviruses - Treatment

- Supportive
- IV ribavirin not effective
- Serum immunotherapy not effective
- Contact and respiratory isolation
- Education of people

Ebola Virus

- People exposed by direct contact with blood or body fluids
- Spread through personal contact – family, friends and medical workers
- Contaminated needles and surgical instruments
- Barrier techniques

Questions?